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WO 02/062814 A1

(54) Title: INHIBITORS OF GLYCOSYLTRANSFERASE ENZYMES

(57) Abstract: The subject invention provides compounds and methods of producing compounds, which are useful inhibitors of glycosyltransferase enzymes. These compounds represent a new class of glycosyltransferase inhibitors and are potent inhibitors of sialyltransferases. The subject invention also provides methods of treating diseases or conditions associated with glycosyltransferases. Methods of modulating the activity of glycosyltransferases are also provided.

INTERNATIONAL SEARCH REPORT

Intern: I Application No
PCT/US 02/03348

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07H19/04 C07H19/06 C07H19/16		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07H		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	SUN, H. ET AL: "Synthesis of a new transition-state analog of the sialyl donor. Inhibition of sialyltransferases" TETRAHEDRON LETTERS (2001), 42(13), 2451-2453, 26 March 2001 (2001-03-26), XP004232269 whole document ---	1-20
X	LESCOP C ET AL: "Synthesis of Novel Nucleosides with a Fused Cyclopropane Ring Substituted by a Hydroxymethyl Group" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 56, no. 19, May 2000 (2000-05), pages 2995-3003, XP004198009 ISSN: 0040-4020 whole document --- -/--	1-15
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents :		
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p> </div> </div>		
Date of the actual completion of the international search <div style="text-align: center; font-weight: bold;">1 July 2002</div>		Date of mailing of the international search report <div style="text-align: center; font-weight: bold;">17/07/2002</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center; font-weight: bold;">Klein, D</div>

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Internat Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GILLESPIE R J ET AL: "THE REACTION OF DIAZOALKANES WITH THIOPHEN" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY. LETCHWORTH, GB, vol. 7, 1979, pages 2624-2628, XP000196859 ISSN: 1472-7781 table 1	1-5
X	AL DULAYYMI A R ET AL: "Pyridazines by addition of diazoalkanes to 1-bromo- and 1,2-dibromocyclopropenes" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 54, no. 42, 15 October 1998 (1998-10-15), pages 12897-12906, XP004134784 ISSN: 0040-4020 compounds 4,16,23,31,32,34,35	1-5
X	TUFARIELLO J J ET AL: "THE SYNTHESIS AND CYCLOADDITION REACTIONS OF 3-AZABICYCLOU3.1.0 HEX-2-ENE 3-OXIDE AND 3-AZABICYCLOU3.2.0HEPT-2-ENE 3-OXIDE. HIGHLY STRAINED BICYCLIC NITRONES" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 28, no. 3, 1987, pages 267-270, XP002026036 ISSN: 0040-4039 compounds 10a, 11a	1,4-6, 8-15
X	EZQUERRA J ET AL: "4-Benzyl-2,3-didehydroproline as a Homochiral Template for Michael Additions. Synthesis of Enantiopure alpha-Allokainoids, beta-Kainoids, 2,3-Methanoprolines and other 3,4-Disubstituted Prolines" TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 7, no. 9, 1 September 1996 (1996-09-01), pages 2613-2626, XP004048335 ISSN: 0957-4166 compound 15	1-15
X	US 4 235 921 A (ACHINI ROLAND ET AL) 25 November 1980 (1980-11-25) examples 2,3	1-3, 8-10,12, 15
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INTERNATIONAL SEARCH REPORT

Intern: Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DIAZ M ET AL: "Enantioselective Synthesis of Novel Homochiral alpha-Substituted (S)-Isoserine Derivatives. Incorporation of this Amino Acid in a Highly Conformationally Constrained Dipeptide Surrogate"</p> <p>TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 7, no. 12, 1 December 1996 (1996-12-01), pages 3465-3478, XP004070821</p> <p>ISSN: 0957-4166</p> <p>compounds 5, 20a, 21a, 21b, 22</p>	1-15
X	<p>HERCOUET A ET AL: "First Asymmetric Synthesis of (-)-(2S, 3R)-Methanoprolin"</p> <p>TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 7, no. 5, 1 May 1996 (1996-05-01), pages 1267-1268, XP004047682</p> <p>ISSN: 0957-4166</p> <p>compound 7</p>	1,3-6, 8-10, 12-15
X	<p>MARINOZZI, MAURA ET AL: "Synthesis and biological evaluation of 6-carboxy-3,4-methanoprolines, new rigid glutamate analogs"</p> <p>FARMACO (1995), 50(5), 327-31 , 1995, XP002203397</p> <p>compounds 7,8,13,14</p>	1,3-6, 8-10, 12-15
X	<p>PRINZBACH, HORST ET AL: "Photoisomerisierung des Cyclohexadien-(1,3)-dicarbonsäure-(1,4)-dimethylesters zu Bicyclo[3.1.0]hexen Derivativaten"</p> <p>CHEM. BER. (1965), 98(7), 2201-20, 1965, XP001083605</p> <p>compounds XI, XV, XXII</p>	1,3-5
X	<p>MACINNES, IAIN ET AL: "Latent inhibitors. Part 3. The inhibition of lactate dehydrogenase and alcohol dehydrogenase by cyclopropane-containing compounds"</p> <p>J. CHEM. SOC., PERKIN TRANS. 1 (1983), (11), 2771-6 , 1983, XP001084946</p> <p>compounds 2 and 3</p>	1,2, 7-11,15
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GILBERT, JOHN C. ET AL: "Competitive sigmatropic hydrogen shifts in bicyclo'3.1.0!hex-2-ene-6-endo carboxaldehydes" J. ORG. CHEM. (1976), 41(24), 3883-91 , 1976, XP002203399 compound 1b ---	1,2,4,5
X	GASSMAN, P. G. ET AL: "The electrolytic decarboxylation of cis- and trans-bicyclo-'3.1.0!hexane-3-carboxylic acids" J. AM. CHEM. SOC. (1966), 88(10), 2252-7, 1966, XP001079500 compounds 5-8,11-12 ---	1,3
X	MCDONALD, RICHARD N. ET AL: "Strained ring systems. IX. Preparation of some 5-substituted bicyclo'3.1.0!hexane-1-carboxylic acids" J. ORG. CHEM. (1970), 35(8), 2666-9 , 1970, XP001079761 compounds 9,12,19 ---	1,3
X	BOSWELL, R. F. ET AL: "1,4-Transannular nitrogen to carbon rearrangement following intramolecular carbenoid insertion. Formation of 6-trans-styryl-3- azabicyclo'3.1.0!hexane" J. ORG. CHEM. (1977), 42(13), 2342-4 , 1977, XP002203400 whole document ---	1,2
X	LAUTENS, MARK ET AL: "Studies in the Directed Cyclopropanation of.alpha.-Allenic Alcohols" J. AM. CHEM. SOC. (1994), 116(19), 8526-35 , 1994, XP001084086 compounds 30d,31a,31b on page 8531 ---	1,5
X	BARRACLOUGH, PAUL ET AL: "The proton nuclear magnetic resonance spectra of 6-substituted bicyclo'3.1.0!hex-2-enes" J. CHEM. SOC., PERKIN TRANS. 2 (1982), (6), 651-6 , 1982, XP002203401 whole document --- -/--	1,3

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Intern: Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>AVRAM ET AL.: "Eine Umlagerung des Tricyclo'4.2.0.0 2,5!octan-Systems in das Tricyclo'4.2.0.0 2,4!octan System"</p> <p>CHEM. BER., vol. 102, 1969, pages 4008-4016, XP002203402 Compound 27 on page 4013</p> <p>---</p>	1,3
X	<p>SCHARF H-D. ET AL.: "Synthese und Eigenschaften der Semiquadratsäure und ihrer Alkalisalze (Moniliformin)."</p> <p>CHEM. BER., vol. 111, 1978, pages 168-182, XP002203405 Compounds 13,14 on page 172 & 179</p> <p>---</p>	1,3
X	<p>WIBERG, KENNETH B. ET AL: "1,2-Bridged cyclopropenes"</p> <p>J. AM. CHEM. SOC. (1991), 113(21), 7969-79 , 1991, XP001084087 page 7972 -page 7975</p> <p>---</p>	1
X	<p>DEHMLow E.V. ET AL.: "1,3-Dipolare Additionen von Tetrachlorocyclopropen mit Diazoalkanen und Arylaziden."</p> <p>J. CHEM. RES, MINIPRINT, 1978, pages 582-590, XP002203404 page 585; examples A,B</p> <p>---</p>	1
X	<p>BAIRD S.: "The intramolecular interaction of cyclopropylidenes with organic sulphides."</p> <p>J. CHEM. RES, MINIPRINT, vol. 11, 1981, pages 4062-4082, XP002203403 page 4068, line 4,5</p> <p>---</p>	1
A	<p>US 5 770 407 A (HAYASHI TAKASHI ET AL) 23 June 1998 (1998-06-23)</p> <p>-----</p>	

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, only a few examples falling into the scope of the claims have been cited.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/03348

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4235921	A	25-11-1980	AU 2019776 A	08-06-1978
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